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(54) Title: ANTHELMINTIC COMPOSITION CONTAINING RAFOXANIDE AND FENBENDAZOLE

(57) Abstract

An anthelmintic composition for oral administration comprises an amount of rafoxanide, suitably 1.5-15 % w/v, in admixture with an amount of fenbendazole, suitably 1.0-10 % w/v, effective to achieve an elevated plasma level of an active sulphur oxide metabolite of fenbendazole following administration to bovines, caprines and ovines, relative to fenbendazole when administered alone. The active ingredients are preferably micronised with greater than 98 % of the particles having an average particle size less then 20 μm. The anthelmintic efficacy of the fenbendazole is potentiated in the presence of rafoxanide without significantly increasing any toxic *sequelae*.

anthelmintic composition containing rafoxanide and fenbendazole

This invention relates to compositions useful in the treatment and prevention of helminth infestation in non-human animals, more especially in animals of the bovine, caprine and ovine species. More particularly, the invention relates to compositions useful in the treatment of helminth infestations including fasciolides, flukes, in particular liver flukes and nematodes in bovines and ovines.

Rafoxanide (N-[3-chloro-4-(4-chlorophenoxy)-phenyl]-2-hydroxy-3,5-diiodo benzamide) is a known fasciolicide. Fenbendazole ([5(phenylthio)-1H-benzimidazol-2-yl]carbamic acid methyl ester) is a benzimidazole derivative which is known to be useful in the treatment of helminthiasis, more especially, as a nematocidal agent. Each of rafoxanide and fenbendazole is poorly soluble in many pharmaceutically acceptable solvents.

EP-A 0 202 568 describes and claims compositions containing rafoxanide and optionally various anthelmintic benzimidazoles, including fenbendazole, in association with a solvent selected from dimethyl isosorbide and glycofurol. Such compositions are indicated to overcome the problems of the art. It is stated that administration of rafoxanide with or without an anthelmintic benzimidazole derivative in a convenient dosage form, e.g., by rumen injector or oral applicator, is hindered by the extremely low solubility of each component in nearly all pharmaceutically acceptable solvents or the high viscosity of any resulting solution or suspension.

Helminth infestation is a major problem in ruminant animals, especially those on pasture. The animals must be rounded up for dosing. In the case of sheep, the animals may have to be rounded up over a wide area.

Rafoxanide and fenbendazole are both known to be taken up by the tissues, but additionally to persist in the bloodstream of ruminants and thus the amounts of rafoxanide and fenbendazole must be carefully

selected so as to avoid the occurrence of toxic *sequelae*, especially in the case of animals which are slaughtered for human consumption. Fenbendazole and its metabolites persist in blood for approximately 4-5 days and in tissues for approximately 14 days. However, in the case of rafoxanide, there are conflicting reports in the literature on the persistence of rafoxanide in blood ranging from a period of a few days to 28 days and in some cases for as long as 56 days. Rafoxanide binds strongly to protein in the blood and although levels persist in blood for some time, in many cases, corresponding tissue levels are not detectable.

There is a need for an effective anthelmintic agent which can be administered as a single dose and which can achieve levels of active agent sufficient to treat helminth infestation, while avoiding toxic *sequelae*.

It is known that fenbendazole is metabolised in the body to fenbendazole sulphoxide and thence to fenbendazole sulphone. The sulphoxide is the chemical entity responsible for the majority of the nematocidal activity. The sulphone is non-active anthelmintically, but is formed by conversion from the sulphoxide.

The invention provides an anthelmintic composition for oral administration, comprising an amount of rafoxanide in admixture with an amount of fenbendazole effective to achieve an elevated plasma level of an active sulphur oxide metabolite of fenbendazole following administration relative to fenbendazole when administered alone.

Preferably, the active metabolite of fenbendazole is fenbendazole sulphoxide, which, as indicated above, is the chemical entity mainly responsible for the nematocidal activity of fenbendazole.

Further, preferably, the rafoxanide is present in an amount of 1.5 to 15% w/v and the fenbendazole is present in an amount of 1.0 to 10% w/v.

Suitable amounts for the respective active ingredients are as follows:

Rafoxanide % w/w	Fenbendazole % w/w
1.5	1.0
3.0	2.0
4.5	3.0
6.0	4.0
7.5	5.0
9.0	6.0
10.5	7.0
12.0	8.0
13.5	9.0
15.0	10.0

Further, preferably, the rafoxanide is administered at a dose rate in the range 7.5-15.0 mg/kg body weight and the fenbendazole is administered at a dose rate in the range 5.0-10.0 mg/kg body weight.

Suitable dose rates (mg/kg body weight) for the respect active ingredients are as follows:

Rafoxanide mg/kg	Fenbendazole mg/kg
7.50	5.0
11.25	7.5
12.00	8.0
15.00	10.0

In a particularly preferred embodiment, each of the active ingredients is micronised.

The rafoxanide preferably has a particle size range wherein at least 99% by weight has an average particle size less than 20μm, at least 90% by weight has an average particle size less than 10μm and at least 55% by weight has an average particle size less than 5μm.

The fenbendazole preferably has a particle size range wherein at least 98% by weight has an average particle size less than 20μm, at least 90% by weight has a particle size less than 15μm and at least 50% by weight has a particle size less than 5μm.

The composition according to the invention is preferably in the form of a suspension.

Preferably, the suspension includes as a suspending agent a gum and/or a pharmaceutically-acceptable, polymeric material with the requisite properties.

A suitable gum is xanthan gum.

A suitable polymeric material is polyvinylpyrrolidone also known as Povidone.

The suspension may also include one or more auxiliary agents selected from a buffering agent, a dispersing agent, a wetting agent, an anti-foaming agent, a preserving agent and a colouring agent *secundem artem*.

The pH of the suspension is suitably in the range 4.5-5.5.

Suitable buffering agents include citric acid monohydrate and disodium hydrogen phosphate or sodium citrate.

Suitable dispersing agents include colloidal silicon dioxide such as that sold under the Trade Mark Aerosil 200 and/or a non-ionic surfactant such as a polyoxyethylene derivative of a sorbitan ester marketed as Polysorbate 20.

A suitable wetting agent is propylene glycol.

A suitable antifoaming agent is simethicone.

Suitable preserving agents include hydroxybenzoate preservatives such as that sold under the Trade Marks Nipasept sodium, Nipasol and Nipagin M.

Suitable colouring agents are any colouring agent suitable for oral administration.

The invention also provides a method of treating or preventing helminth infestation in a ruminant animal, which comprises administering to said animal a composition as hereinbefore defined.

The composition and method according to the invention are especially suitable for the treatment of helminth infestation, including fluke infection in cattle and sheep.

The invention will be further illustrated by the following Examples.

Example 1

A suspension containing rafoxanide and fenbendazole was prepared having the following composition:

Ingredient		Amount (% w/v)
Rafoxanide B.P. (Vet.)		4.5
Fenbendazole		3.0
Citric acid monohydrate B.P.		1.0
Disodium hydrogen phosphate B.P.		3.8
Aerosil 200		0.55
Povidone B.P.		1.5
Xanthan gum N.F.		0.3
Propylene glycol B.P.		5
Polysorbate 20 B.P.		0.5
Simethicone emulsion (PD30) USP XXI		0.2
Nipasept sodium (BP components)		0.14
Chlorophyll WSI E 140		0.15
Water	to	100 ml

in the following manner.

For a 1,800 litre batch, a stainless steel tank is filled to *circa* the 1,400 litre mark with deionised water. The Nipasept sodium, citric acid monohydrate, disodium hydrogen phosphate and chlorophyll are added followed by thorough mixing with a Silverson EX (Silverson EX is a Trade Mark) fine shear head. The mixer is switched off and the Aerosil 200 is added and the mixture is allowed to settle for *circa* 30-60 minutes. The xanthan gum and povidone are blended and gradually added to the main tank.

The Polysorbate 20 and propylene glycol are weighed into a separate 500 litre tank. The rafoxanide and the fenbendazole are added

to the latter tank and mixed together with ~50-100 litres of deionised water by means of a Silverson EX coarse shear head. To the latter mixture is added the simethicone emulsion and the mixture is mixed well to ensure that all of the rafoxanide and fenbendazole is thoroughly wetted. The total minimum mixing time is approximately 30 minutes.

When the Aerosil has dispersed in the main tank, the mixer is switched on and the rafoxanide-fenbendazole mixture is added to the main tank with continuous mixing during the transfer process. The final mixture is allowed to settle for at least about 1 hour or, indeed, overnight and then is made up to the 1,800 litre mark with deionised water.

Each of the active ingredients is micronised to achieve an average particle size range as hereinbefore specified. The pH of the suspension prepared can be 5 $\pm$ 0.5. The fenbendazole was obtained from Cipla Ltd., Bombay, India.

In vivo experiment.

An experiment was carried out to investigate the pharmacokinetics of rafoxanide and fenbendazole when given singly and in combination to lambs.

Twelve lambs aged approximately seven months which had been reared in a large shed on expanded metal floors and which were helminth free were divided randomly into three groups of four. On day 0 of the experiment the lambs were weighed carefully, and each group treated separately with the following treatments.

Group 1 - Fenbendazole 3% at a dose rate of 7.5 mg/kg.

Group 2 - Rafoxanide 4.5% at a dose rate of 11.25 mg/kg.

Group 3 - A mixture of fenbendazole 3% and rafoxanide 4.5% at dose rates of 7.5 mg/kg and 11.25 mg/kg, respectively.

The mixture for Group 3 corresponded to the suspension prepared in Example 1. Suspensions of active ingredient were also administered to Group 1 and Group 2 which, in each case, corresponded to a suspension as prepared in Example 1 but without rafoxanide and fenbendazole, respectively.

Sampling. Blood samples were taken from the lambs before dosing at day 0, and afterwards at day 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 14, 21 and 28. The samples were centrifuged, plasma removed and stored at -20°C until analysis. Samples taken from Groups 1 and 3 were analysed for fenbendazole and its metabolites up to day 5. All samples from Groups 2 and 3 for rafoxanide concentrations were analysed.

Determination of fenbendazole and metabolites. The method used for extraction of the compounds from plasma was that of Barker, S.A. *et al.* ((1986); Anal. Biochem., *155*, 112-118). Thus, the plasma was made alkaline by addition of ammonium hydroxide and applied to a Chem-Elut (Chem-Elut is a Trade Mark) column. Fenbendazole was eluted from the column by addition of methylene chloride and the eluates evaporated to dryness in an atmosphere of nitrogen. The eluates were then dissolved in mobile phase and chromatographed using reverse phase HPLC and UV detection under conditions described by Bull, M.S. and Shume G.R.E. ((1987); J. Pharmaceutical and Biochem. Analy. *5*, 501-508).

Determination of plasma rafoxanide. The method used was that of Blanchflower, W.J., *et al.* ((1990); J. Liq. Chromatog. *13* (8) 1595-1609) which basically consists of separation of rafoxanide from the plasma proteins to which it binds by extraction with acetone ether and acetonitrile, and subsequent injection on to an HPLC system with UV detection set at 282 nm. The method is specific and sensitive with a lower limit of detection of 0.1 μg/ml.

Statistical analysis. The mean plasma concentration of rafoxanide and fenbendazole and its metabolites was calculated for each group and sampling occasion. Differences between mean concentrations at each date were compared by t test. Areas Under Curve (AUC) were calculated by the trapezoidal method of Gibaldi, M and Perrier, D. ((1982); "Pharmacokinetics" published by Mancel Dekker, New York) from time 0 until the time of non-detectable concentration or the last observation, whichever occurred first.

Results.

(1) Plasma rafoxanide concentrations.

The results are summarized in Tables 1 (Group 2 (rafoxanide only)) and 2 (Group 3 (rafoxanide and fenbendazole)) and in Fig. 1. Plasma concentrations are expressed in µg/ml.

TABLE 1

Time (days)

Lamb No.	0	0.5	1	1.5	2	2.5	3	4	5	7	14	21	29
5	0	38.1	51.1	62.8	59.9	55.7	55.1	45.3	54.7	54.1	30.4	21.9	10.7
6	0	20.1	30.1	17.6	34.6	53.0	57.2	68.1	33.6	19.6	5.4	4.4	4.6
7	0	25.2	41.2	51.4	49.0	47.7	47.5	48.3	41.3	39.9	26.0	16.2	9.6
8	0	30.3	43.6	47.4	45.5	50.5	49.3	52.8	44.2	34.7	21.9	13.6	6.0
Mean	0	28.4	41.5	44.8	47.3	53.1	52.3	53.6	43.5	37.1	20.9	14.0	7.7
SD*	0	6.6	7.5	16.7	9.0	2.9	3.9	8.7	7.6	12.3	9.5	6.3	2.5

* SD = Standard deviation

TABLE 2

Time (days)

Lamb No.	0	0.5	1	1.5	2	2.5	3	4	5	7	14	21	29
9	0	24.7	39.7	63.4	62.3	61.7	53.3	50.2	51.1	50.4	25.2	13.9	4.2
10	0	13.8	38.5	62.0	54.2	55.1	51.4	46.2	46.8	36.0	18.7	8.2	1.5
11	0	23.2	34.0	41.0	37.1	37.1	40.8	30.8	28.1	20.1	9.5	4.4	0.9
12	0	29.4	44.0	61.4	47.8	48.2	57.3	63.2	54.6	47.1	30.7	20.3	9.3
Mean	0	22.8	39.1	56.9	50.4	55.5	50.7	47.6	45.2	38.4	21.0	11.7	3.9
SD*	0	5.7	3.6	9.2	9.2	11.6	6.1	11.6	10.2	11.8	7.9	6.0	3.3

* SD = Standard deviation

Areas Under Curve

Group 2 (rafoxanide only)	707.15 ± 226.1
Group 3 (rafoxanide and fenbendazole)	683.62 ± 238.4

t = 0.143; no significant difference

There were no significant differences between plasma rafoxanide concentration (µg/ml) at each sampling date point, and between the AUC for each group.

* * * *

(2) Plasma fenbendazole concentrations.

A. Fenbendazole parent compound.

The results are summarized in Tables 3 (Group 1 (fenbendazole only)) and 4 (Group 3 (fenbendazole and rafoxanide mixture)) and in Fig. 2.

TABLE 3

Time (hours)

Lamb No.	0	12	24	36	48	60	72	96
1	0	.185	.197	.19	.053	.064	.043	.021
2	0	.192	.209	.186	.120	.073	.055	.023
3	0	.110	.098	.129	.082	.051	.029	0
4	0	.105	.097	.078	.046	.062	.009	0
Mean	0	.148	.15	.146	.075	.063	.034	.011
SD*	0	.041	.05	.046	.029	.008	.017	.011

* SD = Standard deviation

TABLE 4

Lamb No.	Time (hours) 0	12	24	36	48	60	72	96
9	0	.16	.14	.194	.114	.072	.046	.025
10	0	.16	.128	.103	.1	.073	.049	0
11	0	.137	.107	.144	.066	.043	0	0
12	0	.23	.157	.189	.117	.107	.054	0
Mean	0	.171	.133	.157	.099	.074	.037	.0063
SD*	0	.035	.018	.036	.02	.02	.02	.01

* SD = Standard deviation

Mean AUC Group 1 = 6.837 ± 2.09
Mean AUC Group 3 = 7.332 ± 1.54

$t = 0.38$; no significant differences

As can be seen from the above tables and Fig. 2 there were no significant differences between concentrations of fenbendazole parent compound and AUC in either the group given fenbendazole only and that given the mixture of fenbendazole and rafoxanide.

* * * *

B. Fenbendazole sulphoxide.

The results are summarized in Tables 5 (Group 1 (fenbendazole only)) and 6 (Group 3 (fenbendazole and rafoxanide mixture)) and Fig. 3.

TABLE 5

Time (hours)

Lamb No.	0	12	24	36	48	60	72	96
1	0	.169	.3	.31	.125	.191	.127	.049
2	0	.155	.24	.286	.224	.174	.112	.044
3	0	.089	.166	.264	.2	.137	.092	.023
4	0	.17	.192	.193	.127	.085	.034	.013
Mean	0	.15	.23	.26	.169	.15	.09	.03
SD*	0	.033	.05	.04	.04	.04	.04	.014

* SD = Standard deviation

TABLE 6

Time (hours)

Lamb No.	0	12	24	36	48	60	72	96
9	0	.147	.269	.377	.305	.23	.172	.071
10	0	.182	.263	.322	.31	.248	.172	.061
11	0	.22	.27	.314	.218	.133	.073	.02
12	0	.285	.352	.466	.339	.311	.178	.067
Mean	0	.21	.29	.37	.293	.23	.15	.05
SD*	0	.05	.04	.06	.05	.06	.04	.02

* SD = Standard deviation

Mean AUC Group 1 = 12.453 ± 2.43
Mean AUC Group 3 = 18.77 ± 3.3

$t = 3.0389$ (DF6) $p < 0.05$

As can be seen from Tables 5 and 6 there were differences between the plasma fenbendazole sulphoxide concentrations in each group, with that of the group given the anthelmintic mixture the greatest. Although there was a strong trend throughout, only at 36 and 48 hrs post dosing were the differences statistically significant ($p < 0.05$ and < 0.01 respectively).

Taken as a whole the differences in AUC (which can be seen in Fig. 3) were significant ($p < 0.05$), indicating that the presence of rafoxanide had altered the rate of metabolism of fenbendazole and its sulphoxide metabolite, although the resultant alteration would be of anthelmintic benefit since the sulphoxide is the chemical responsible for the majority of the nematocidal activity.

* * * *

C. Fenbendazole sulphone. The results are summarized in Tables 7 (Group 1 (fenbendazole only)) and 8 (Group 3 (fenbendazole and rafoxanide mixture)) and in Fig. 4.

TABLE 7

Time (hours)

Lamb No.	0	12	24	36	48	60	72	96
1	0	.021	.064	.095	.059	.109	.103	.078
2	0	.021	.059	.086	.106	.106	.106	.067
3	0	.009	.032	.074	.091	.097	.104	.067
4	0	.033	.065	.078	.087	.080	.059	.053
Mean	0	.021	.055	.083	.086	.098	.093	.066
SD*	0	.088	.01	.008	.01	.01	.01	.008

* SD = Standard deviation

TABLE 8

Time (hours)

Lamb No.	0	12	24	36	48	60	72	96
9	0	.026	.072	.12	.166	.152	.153	.133
10	0	.031	.06	.116	.161	.174	.186	.145
11	0	.031	.08	.113	.122	.103	.089	.059
12	0	.04	.105	.158	.192	.215	.186	.162
Mean	0	.032	.079	.127	.16	.161	.154	.125
SD*	0	.005	.016	.018	.025	.04	.03	.039

* SD = Standard deviation

Mean AUC Group 1 = 6.459 ± .577
Mean AUC Group 3 = 10.779 ± 2.17

t = 3.767 (DF6) p <0.01

As indicated above, the sulphone is non active anthelmintically but is formed by conversion from the sulphoxide. Since the sulphoxide concentrations differed between Groups 1 and 3, the sulphone concentrations were also significantly different at all sampling dates after 0 and 12 hours. The resultant AUC were significantly different ($p < 0.01$).

* * * *

Conclusions.

It can be observed from these results that administration of the mixture of rafoxanide and fenbendazole did not alter the pharmacokinetics of rafoxanide from that when rafoxanide is given by itself. The pharmacokinetics of fenbendazole and its metabolites did differ from that of fenbendazole administered by itself in that the plasma concentrations of fenbendazole sulphoxide and sulphone were increased when the mixture was administered. Thus, it can be concluded that administering rafoxanide and fenbendazole in combination in accordance with the invention will potentiate the anthelmintic efficacy of the fenbendazole without significantly increasing any toxic *sequelae*.

CLAIMS:

1. An anthelmintic composition for oral administration, comprising an amount of rafoxanide in admixture with an amount of fenbendazole effective to achieve an elevated plasma level of an active sulphur oxide metabolite of fenbendazole following administration relative to fenbendazole when administered alone.

2. A composition according to Claim 1, wherein the active metabolite of fenbendazole is fenbendazole sulphoxide.

3. A composition according to Claim 1 or 2, wherein the rafoxanide is present in an amount of 1.5 to 15% w/v and the fenbendazole is present in an amount of 1.0 to 10% w/v.

4. A composition according to any preceding claim, wherein the rafoxanide is administered at a dose rate in the range 7.5-15.0 mg/kg body weight and the fenbendazole is administered at a dose rate in the range 5.0-10.0 mg/kg body weight.

5. A composition according to any preceding claim, wherein each of the active ingredients is micronised.

6. A composition according to Claim 5, wherein the rafoxanide has a particle size range wherein at least 99% by weight has an average particle size less than 20μm, at least 90% by weight has an average particle size less than 10μm and at least 55% by weight has an average particle size less than 5μm..

7. A composition according to Claim 5 or 6, wherein the fenbendazole has a particle size range wherein at least 98% by weight has an average particle size less than 20μm, at least 90% by weight has a particle size less than 15μm and at least 50% by weight has a particle size less than 5μm.

8. A composition according to any preceding claim, which is in the form of a suspension.

9. A composition according to Claim 8, which includes as a suspending agent a gum and/or a pharmaceutically-acceptable, polymeric material.

10. A composition according to Claim 9, wherein the gum is xanthan gum.

11. A composition according to Claim 9 or 10, wherein the polymeric material is polyvinylpyrrolidone.

12. A composition according to any preceding claim, which includes one or more auxiliary agents selected from a buffering agent, a dispersing agent, a wetting agent, an anti-foaming agent, a preserving agent and a colouring agent.

13. A composition according to any one of Claims 1-12, for use in treating or preventing helminth infestation in a ruminant animal

14. A composition according to Claim 13, wherein the ruminant animals are cattle or sheep.

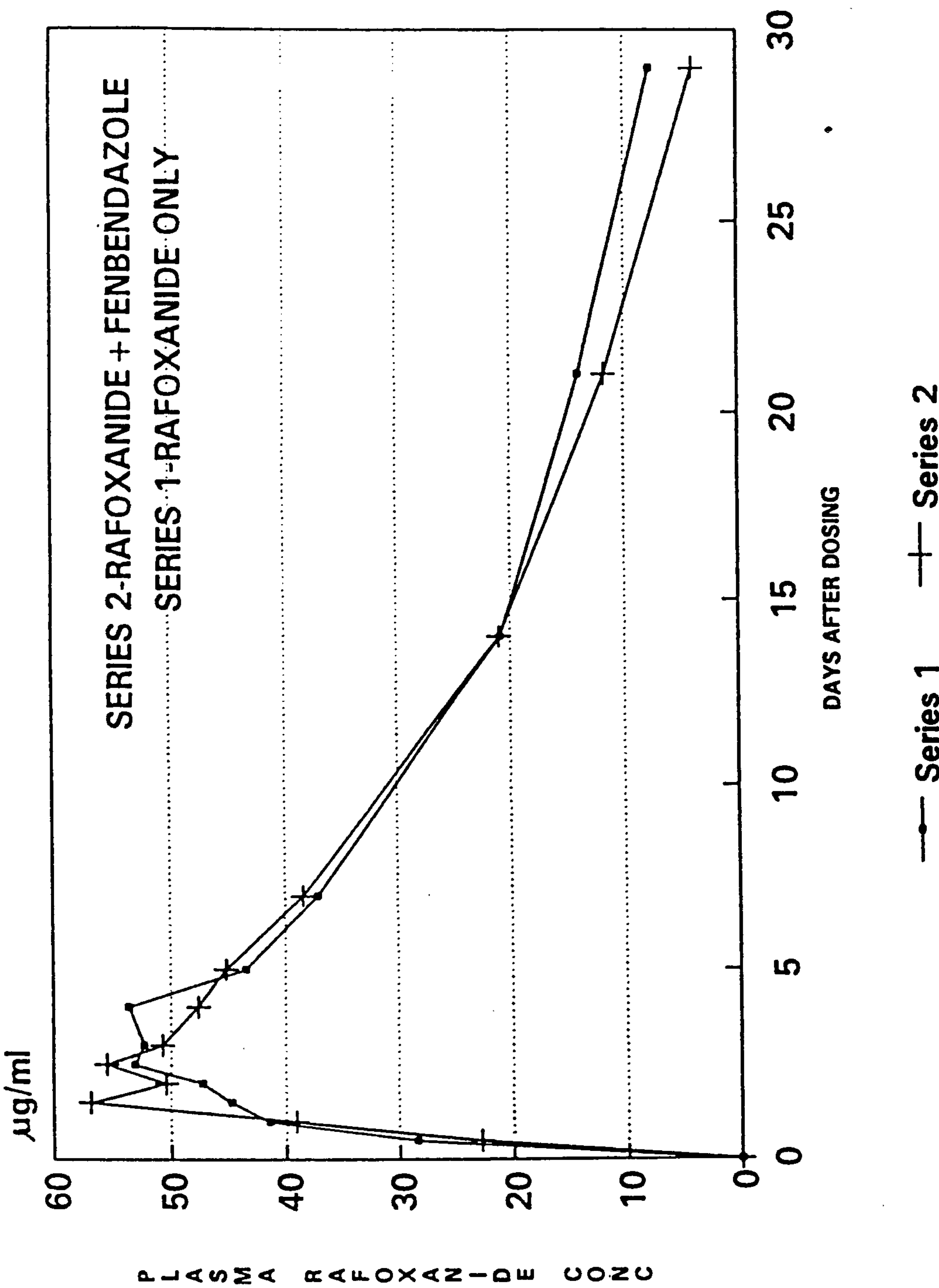
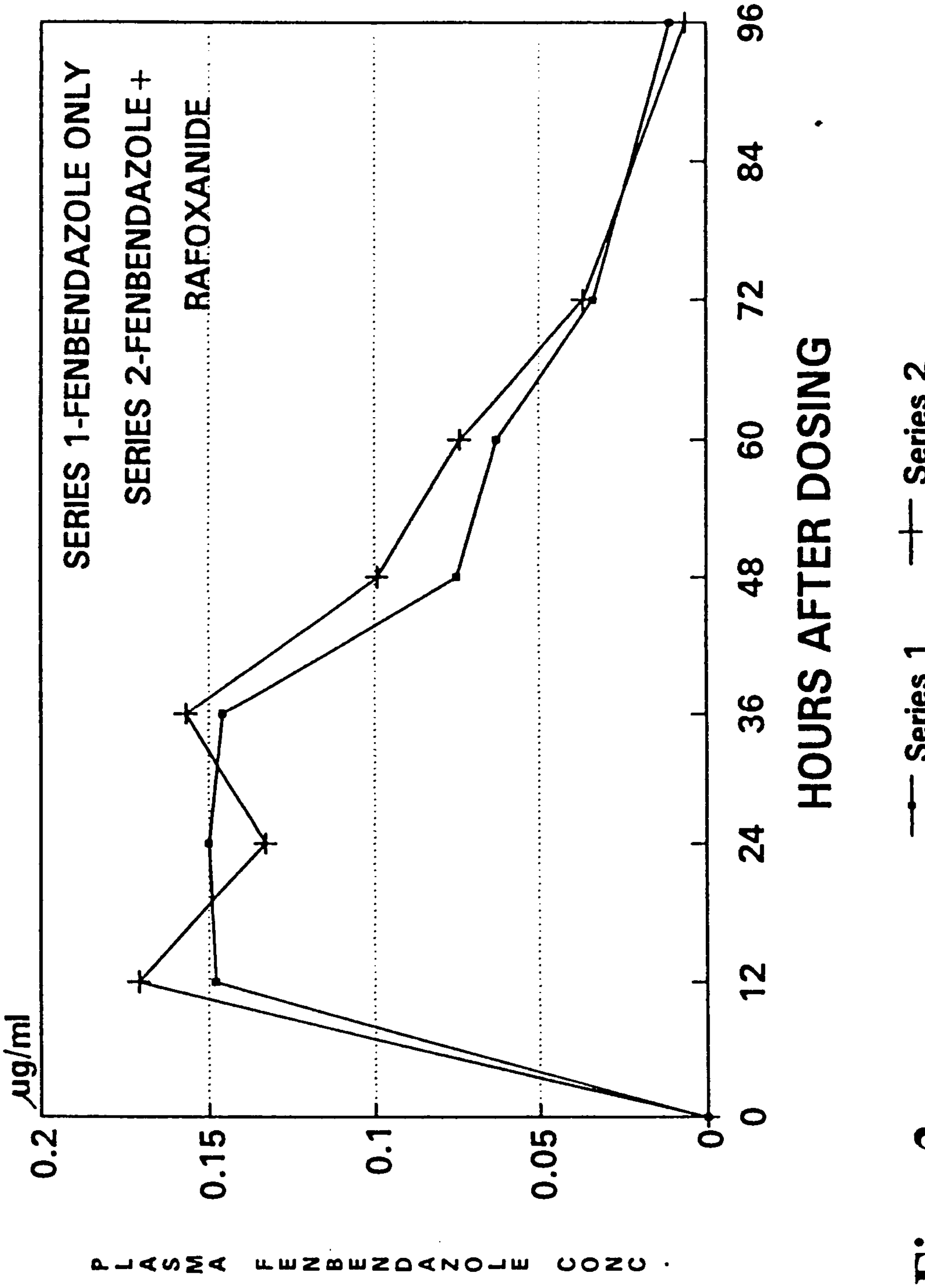
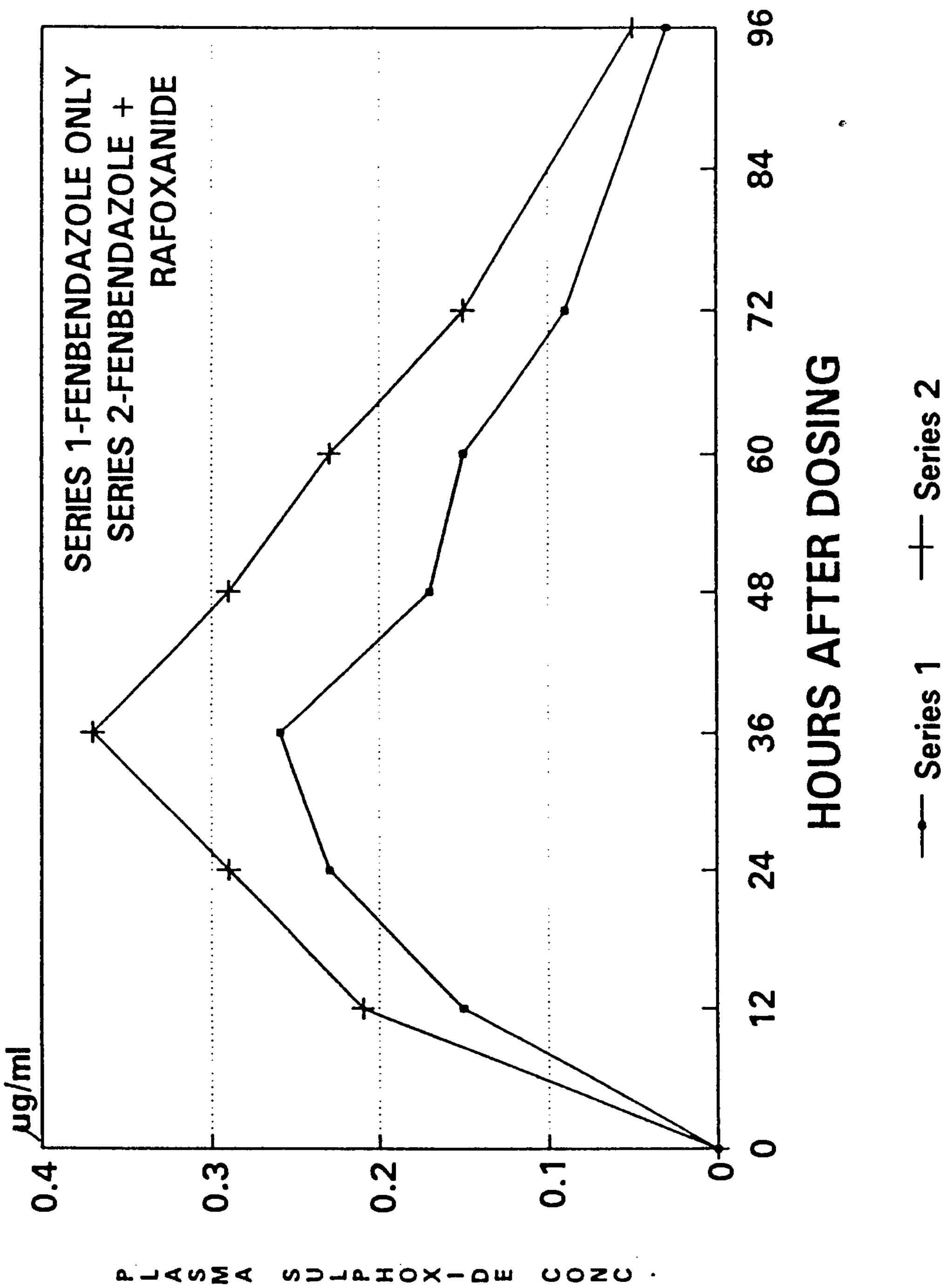

SERIES 2-RAFOXANIDE + FENBENDAZOLE
SERIES 1-RAFOXANIDE ONLY
µg/ml
PLASMA RAFOXANIDE CONC
60
50
40
30
20
10
0
0
5
10
15
20
25
30
DAYS AFTER DOSING
Series 1
Series 2

Fig. 1



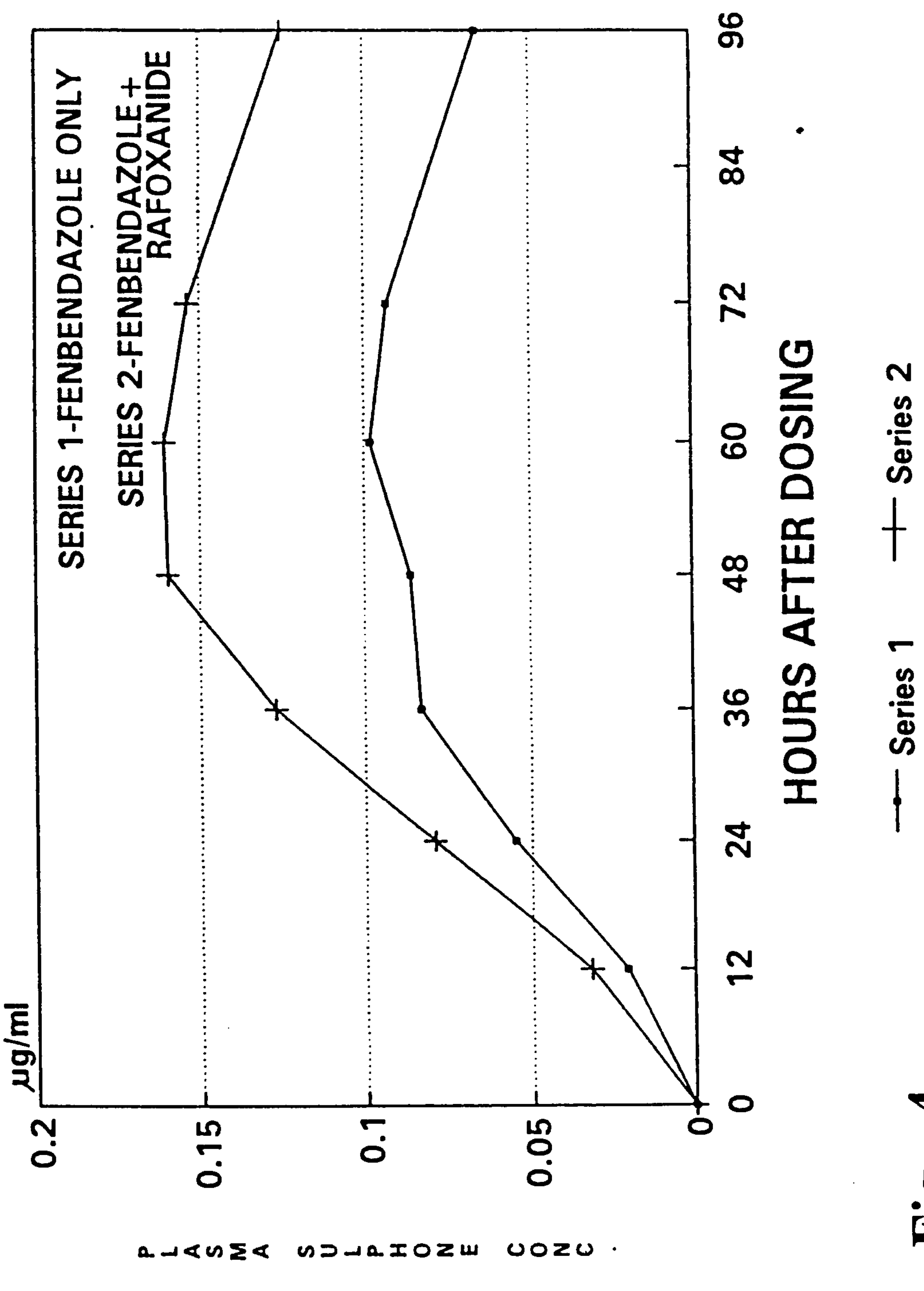
SERIES 1-FENBENDAZOLE ONLY
SERIES 2-FENBENDAZOLE + RAFOXANIDE
µg/ml
0.2
0.15
0.1
0.05
0
PLASMA FENBENDAZOLE CONC.
0
12
24
36
48
60
72
84
96
HOURS AFTER DOSING
Series 1
Series 2

Fig. 2



SERIES 1-FENBENDAZOLE ONLY
SERIES 2-FENBENDAZOLE +
RAFOXANIDE
µg/ml
0.4
0.3
0.2
0.1
0
PLASMA SULPHOXIDE CONC
0
12
24
36
48
60
72
84
96
HOURS AFTER DOSING
Series 1
Series 2

Fig. 3



μg/ml
PLASMA SULPHONE CONC.
0.2
0.15
0.1
0.05
0
0
12
24
36
48
60
72
84
96
HOURS AFTER DOSING
SERIES 1-FENBENDAZOLE ONLY
SERIES 2-FENBENDAZOLE + RAFOXANIDE
Series 1
Series 2

Fig. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IE 93/00059

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 //(A61K31/415,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 202 568 (SYNTEX INC.) 26 November 1985 cited in the application see abstract; claim 16	1
A	INDIAN VET MED J,, VOL. 16, NO. 1, PAGE(S) 34-36, 1992 D'SOUZA P E et al 'CONTROL OF NASAL MYIASIS IN SHEEP WITH RAFOXANIDE' see page 35, line 35 - line 39	1-14
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Leherte, C

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